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I

ECTEINASCIDIN (ET-743) IN HEAVILY PRETREATED REFRACTORY SARCOMAS: PRELIMINARY EVIDENCE OF ACTIVITY

S. Delaloge[1], M. Riofrio[1], E. Brain[2], P. Cottu[3], A. Taamma[4], M. Marty[3], C. Guzman[5], J.L. Misset[1], E. Cvitkovic[4]. [1]Hop Paul Brousse; [2]Centre René Huguenin; [3]Hop St Louis; [4]CAC, France, [5]Pharmamar, Spain.

ET-743 is a tetrahydro-isoquinolone of marine origin, currently in late phase I, early phase II development with neutropenia (N) and thrombocytopenia (T) as limiting toxicities. Fatigue and reversible transaminitis (Tm) were also noticed. Antitumoral activity has been detected during the 24 hours continuous infusion (CI)-every 3 weeks schedule phase I (ASCO 1999, abst 680), which has completed accrual. We report here our current overall experience in treatment-refractory advanced sarcoma patients (pts). Pts charact: Eleven pts (9 soft tissue sarcomas (STS) and 2 osteosarcomas (OS)) received ET-743, 10 at the recommended dose (1500 µg/m²), one at the maximum tolerated dose (1800 µg/m²). 9 of them were treated in the phase I trial, while 2 received ET-743 on a compassionate use basis. Sex: 6 men/5 women, median age: 37 years (16-71), median number of previous chemotherapy regimens: 2 (1-4) (all pts pre-treated with anthracyclines and alkylators); median PS: 1 (0-2), median number of metastatic sites 2 (1-3). Results: Toxicity is evaluable for the 38 given cycles. Grade 3-4 toxicities are acute reversible Tm peaking at day 3-5 (52%), N (39.5%) and T (10.5%). Febrile N occurred in 2 cycles (5%). All 11 pts are evaluable for antitumor activity. Two PR (1 ongoing), 2 MR (2 ongoing) and 3 SD (lasting > 4 months) were observed. Among the 2 osteosarcomas, there was 1 PR and 1 MR. ET-743 is a promising new agent for heavily pre-treated refractory OS and STS. Based on this experience, a phase II program is ongoing, assessing the 1500µg/m²/24-hours CI schedule in such pts.

Please type

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725

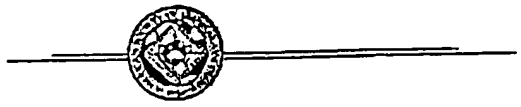
A Phase I and Pharmacokinetic Trial of Ecteinascidin- 743 (ET- 743) Administered as a 72 Hour Continuous Infusion. *David P. Ryan, Jeffrey G. Supko, Joseph P. Eder, H. Lu, Bruce Chabner, Kristin Roper, Paul Baccala, Jill Bonenfant, Glenn Faircloth, C. Guzman, Jose Jimeno, Jeffrey W. Clark. Pharma Mar, S.A., Madrid, Spain.*

(2)

ET-743 is a tetrahydroisoquinoline alkaloid that binds to the minor groove of DNA. Since preclinical studies showed enhancement of tumor growth inhibition with prolongation of exposure, a phase I study of ET-743 administered as a 72 hour i.v. infusion every 21 days was initiated. 15 patients with metastatic solid tumors were enrolled: 9 men, 6 women; median age=52 years; 15/15 with ECOG performance status≤1; 4/15 had>2 prior regimens. The dose has been escalated from 600 mg/m2 to the apparent maximum tolerated dose (MTD) of 1200 mg/m2. Grade 3 transaminitis was not defined as a dose limiting toxicity (DLT). There were no DLTs among the 6 patients entered at the first two dose levels, but 2 patients on dose level 2 had grade 3 transaminitis. At dose level 3, 9 patients have received 15 cycles of ET-743. 2 patients had grade 4 and 5 patients had grade 3 transaminitis. AST/ALT levels increased on days 3-5, peaked on days 7-9, and returned to baseline by day 21. 1 patient at dose level 3 experienced grade 4 rhabdomyolysis, grade 4 neutropenia, grade 3 thrombocytopenia and acute renal failure during the 2nd cycle of therapy. Another patient at dose level 3 had grade 3 neutropenia. ET-743 plasma profiles were biphasic with a mean biological half-life of 59.9 ± 33.4 hr. Mean values of the total body clearance (CL), peak plasma concentration (Cmax) and area under the curve (AUC) are summarized below.

Dose Level (µg/m2/72hr	CL (L/h/m2)	Cmax (pg/ml)	AUC (ng*hr/ml)	Patients with DLT
1.600	29.4	283	12.0	0/3
2.900	35.7	581	24.7	0/3
3.1200	14.1	908	42.7	3/9

Activity was assessed by CT and PET scans before treatment and after every 2 cycles of therapy, as well as PET scan during week 2 of cycle 1. There was evidence of activity in 2 patients at dose level 3. A patient with mesothelioma showed a response by PET and CT scans that has not yet met criteria for PR. A patient with choroidal melanoma also showed reduced fluorodeoxyglucose uptake by PET scan after one cycle of therapy. Further refinement of the MTD and continued assessment of patients is ongoing.



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FINAL RESULTS OF A PHASE I STUDY OF ECTEINASCIDIN-743 (ET-743) 24 HOURS (h) CONTINUOUS INFUSION (CI) IN ADVANCED SOLID TUMORS (AST) PATIENTS (pts). E. Cvitkovic[1], M. Riofrio[1], P. Goldwasser[1], S. Delaloge[1], A. Taamma[1], J. Beljean[2], J.M. Jimeno[3], B. Mekranter[1], C. Guzman[3], B. Brain[4], J.L. Misset[1]. [1]Hop P. Brousse, Villejuif, France; [2]The Netherlands Cancer Institute; [3]Pharma Mar S.A., Spain; [4]Centre R. Huguenin, Saint-cloud, France.

ET-743 is a novel minor groove DNA binding agent specific to guanine-cytosine rich regions with activity in murine tumor models and human cancer xenografts. Bone marrow and hepatic toxicities were dose limiting in animals. The results of phase I study with ET-743 CI 24 h given every 3 weeks, in AST pts are presented. Between 5/96 and 11/98, 49 pts received a total of 148 cycles (cy) over 9 dose levels (DL) (50-1800 µg/m²), median number of cy/pts = 2 (1-8). Median age 59 (19-75) F/M= 28/21, median ECOG PS 1 (1-2). Tumor types: colorectal (12), sarcoma (11), breast (7), ovary (6), renal (3),bladder (2), gastric (2), ACUP (2), larynx (1), melanoma (1), 2 pts had both sarcoma and breast cancer. Acute nausea/vomiting (grade 2) were seen from the 600 µg/m² DL. Emesis was easily controlled. Reversible transaminases elevation peaking at days 3-7, back to baseline by day 14 occurred at the 4 highest DL and was never a Dose Limiting Toxicity (DLT). The Maximal Tolerated Dose was 1800 µg/m², with neutropenia and thrombopenia being the DLTs. The Recommended Dose for phase II studies is 1500 mg/m². The table below summarize the severe toxicities (NCI-CTC) by pts and cy observed at the 4 highest DLs:

		Neutropenia		Thrombopenia		Transaminases	
DL	pt/cy	gr 3	gr 4	gr 3	gr 4	gr 3	gr 4
900	3/8	-/-	-/-	-/-	-/-	1/1	-/-
1200	5/19	-/-	-/-	-/-	-/-	2/2	-/-
1500	22/56	3/11	5/12	4/5	2/2	6/18	5/5
1800	4/16	-/5	7/10	-/1	2/3	1/4	2/2

One partial response (PR) was seen in pt with metastatic breast cancer refractory to anthracyclin and docetaxel, another PR was observed in a heavily pretreated pt with metastatic osteosarcoma, with several minor and biological responses also seen in breast, sarcoma and colon, all in pts receiving doses ≥ 1200 µg/m². Phase II trials with ET-743 are warranted. Since treatment is ongoing in 6 pts, final results with all evaluable cy will be presented. PK/PD relationships are presented elsewhere.

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after radiotherapy, for a complete remission rate of 46% (6/18). The median duration of response was 10 months. The median survival of the entire patients population was 9 months with 33% survival rates at 1 year. The patient with AAO is free of descease at 82 months from the beginning of chemotherapy. Vomiting grade 3, hematologic toxicity grade 4 in one patient and grade 3 in two patients were the major complications due to chemotherapy, while nephrotoxicity and neurotoxicity were usually mild.

Conclusion: Our sequential chemo-radiotherapy regimen appears to have significant activity in adults with newly diagnosed high-grade gliomas.

636P Æ-941 (Neovastat), an inhibitor of angiogenesis: Phase I/II lung cancer clinical trial results

M. Rivière[1], J. Latreille[2], P. Falardeau[1], É. Dupont[1]. [1]*Ælema Laboratories Inc., Ste-Foy, G1N 4A8,* [2]*Centre Hospitalier de l'Université de Montréal, H2W 1T8, Canada*

Introduction: Æ-941 is a complex derived from cartilage that has shown both antiangiogenic and antimetalloproteinase activities. Oral administration of Æ-941 (125 mg/kg) resulted in approximately 50–70% reduction in the number of lung metastases using the Lewis Lung Carcinoma mouse model. No signs of toxicity were observed.

Methods: Æ-941 is currently in Phase I/II clinical trials in Canada and in the US for the treatment of lung, prostate and breast cancers. Patients were administered escalating doses (4) of Æ-941 for 12 weeks. Tolerability and clinical benefits (tumor assessment, ECOG, body weight and analgesic consumption combined) were evaluated.

Results: Results obtained from 25 assessable patients of the Phase I/II trial for lung cancer show a trend in favor of a dose/response effect of patients' clinical benefits. Doses ranging between approximately 10 to 80 mg/kg were administered orally. Including the Canadian Special Access Program that started in July 1996 and the ongoing Phase I/II clinical trials, approximately three hundred and thirty (330) patients have been exposed to Æ-941 for up to 20 months without reporting any serious adverse events definitively associated with it.

Conclusions: Oral administration of Æ-941 demonstrates a favorable safety profile and show a positive trend in favor of a dose/response improvement in clinical parameters. Complete results of Phase II lung and Phase I breast and prostate trials will be available Q3-98.

637P In vitro cytotoxicity of Tomudex (TOM) in combination with 5-Fluorouracil (5-FU) and levofolinic acid (LFA) in head and neck and colon cancer cell lines

A. Budillon, D. Barbarulo, E. Di Gennaro, C. Manzo, G. Comella, F. Caponigro. *Istituto Nazionale Tumori G. Pascale, Napoli, Italy*

Tomudex is a pure thymidylate synthase inhibitor, with clinical activity in colorectal cancer and in other solid tumors. TOM has recently been reported to down-regulate the activity of dihydropyrimidine dehydrogenase (DPD), and this implies a potential role for TOM in combination with 5-FU.

We have evaluated the citotoxicity of TOM, 5-FU and LFA, when used in several different schedules in three colon cancer cell lines, (LOVO, GEO and SW620) and in one oral epidermoid carcinoma cell line (KB), using the SRB colorimetric assay.

LFA 5 μM alone had no effect on cell proliferation, while in combination with 5-FU it reduced by about 50% 5-FU IC50 in all tested cell lines, as expected. If 5-FU was added simultaneously to TOM, a slightly additive effect was observed. When LFA, alone or in combination with 5-FU, was added simultaneously to TOM, it significantly inhibited TOM-induced citotoxicity by increasing TOM IC50 up to 30 fold. The same effect was observed if cells were treated with LFA alone or in combination with 5-FU followed 24 hrs later by TOM. In this case TOM IC50 was increased up to 10 fold. When 5-FU alone was followed 24 hours later by TOM, an additive effect was observed. Interestingly, if cells were exposed for 24 hours to TOM and then to 5-FU + LFA, a clear synergism was observed in all tested cell lines, while only an additive effect was shown when 5-FU alone was added, thus indicating an important role for LFA in this schedule-dependent synergistic effect.

In conclusion, our preliminary in vitro studies suggest that LFA does not interfere with TOM cytotoxicity if a 24 hour interval elapses between the two drugs. In addition, this study also indicates that the combination of TOM followed 24 hours later by LFA+5FU is a worth pursuing approach for clinical investigation. Finally, we are currently measuring DPD activity in all tested cell lines in order to find out a possible correlation with in vitro synergistic effect.

638P Resistance to Gemcitabine (GEM) in a Fas-ligand (FasL)-resistant cell line is not dependent on the Fas/Fasl (CD95/CD95L) system

M. Meli[1,2], M. Tolomeo[3], N. D'Alessandro[3], S. Grimaudo[3], G. Rubert[4], G. Papoff[4], L. Rsusa[1], L. Dusonchet[2]. [1]*Institute of Oncology;* [2]*Institute of Pharmacology;* [3]*Chair of Hematology, University of Palermo,* [4]*Institute of Cell Biology, CNR Rome, Italy*

Introduction: The T-cell lymphoma HUT78B1 cells were selected by exposure to a Fas-agonistic Ab and, in contrast to the parental HUT78, are resistant to Fas-mediated apoptosis owing to the expression of both a wild-type and a truncated Fas receptor. HUT78B1 retain sensitivity to apoptosis from various anticancer drugs, but are resistant to the cytidine analog GEM.

Methods and results: Cytotoxicity was evaluated by vitality assay and apoptosis by flow cytometry and fluorescence microscopy. In comparison with HUT78, HUT78B1 exhibited a high (about 100-fold) resistance to the cytotoxic and apoptotic effects of GEM. They were moderately cross-resistant to cytarabine, but retained sensitivity to fludarabine or hydroxyurea. To clarify whether the Fas/FasL system plays a role in the cellular response to GEM, we evaluated the effects of GEM in HUT78 after pretreatment with FasL- (NOK1, NOK2) or Fas-(ZB4, DX2) blocking antibodies or the inhibitor of caspase 8 YVAD-cmk. Overall, we did not observe any clearcut effect of such blocking reagents on GEM-induced apoptosis and cytotoxicity, in spite of an increase in FasL levels after 4 or 8 h of exposure to GEM, as shown by Western blotting assay. However, the apoptotic effects of GEM were suppressed by Z-VAD, a wide spectrum inhibitor of caspases. Finally, HUT78B1 accumulated about 10-fold less SH-GEM than HUT78.

Conclusions: The antitumor effects of GEM on HUT78 cells do not correlate to the Fas/FasL pathway, whereas they seem to be dependent on the caspase cascade. GEM accumulation by the cells might account for the response to GEM in this model. The possible interactions between the Fas/FasL system and chemotherapeutics agents deserve further investigations and might have relevance to cancer therapy. Supported by Eli Lilly.

639P Ecteinascidin-743 (ET-743) 24 hours continous infusion (CI): Clinical and pharmacokinetic phase I study progressive report

M. Riofrio[1], A. Taamma[1], B. Mckranter[1], F. Goldwasser[1], J. Jimeno[2], C. Jasmin[1], J.L. Misset[1], E. Cvitkovic[1]. [1]*FSMSIT, Hôpital Paul Brousse, Villejuif, France;* [2]*Pharma Mar, Madrid, Spain*

Introduction: ET-743, a tetrahydroisoquinoline alkaloid isolated from the Ecteinascidia Turbinata, a minor grove DNA binding agent specific for the guanine rich regions, with potent activity in murine tumor models and in human lines in vitro and in vivo. Bone marrow and liver function toxicity were shown in preclinical studies. A phase I study with ET-743 I.V. 24 hours C.I. every 21 days is ongoing, in solid avanced stages tumors.

Methods: Since may 1996, 31 pts were treated over 9 dose levels (DL) from 50 to 1800 μg/m². Median number of cycles/pts: 2 (1–6), median age: 55 (26–74). F/M: 16/13, ECOG PS: 1 (0–2). Tumor types: colo-rectum (7), ovary (4), sarcoma (7), renal (3), breast (4), bladder (2), larynx (1), gastric (2) and ACUP (1), all refractory to standard chemotherapy. Nausea/vomiting (grade 2) and reversible (4–6 days) transaminase elevation starting 2–4 days after treatment were seen from 600 μg/m² DL. This toxicity is self limiting (resolved by day 7–10). Maximal transaminase (ASAT-ALAT) elevation, and neutropenia, at the five highest DL is shown below (NCIC-CTC)

Dose level μg/m²	Pts/Cy	Neutropenia		Transaminitis	
		Grade 0–2	Grade 3–4	Grade 0–2	Grade 3–4
600	3/6	2/6	-	2/6	
900	3/8	2/8	-	2/7	1/1
1200	5/19	5/19	-	3/17	2/2
1500	4/18	1/9	3/7	1/9	3/7
1800	4/7	2/2	2/5	1/2	3/5

Conclusion: The incidence of reversible grade 4 transaminates and frequency of grade 4 neutropenia suggest that MTD is close to 1800 μg/m²

640P Optimization of tumor suppressor genes delivery using original cationic lipids in malignant mesothelioma cells

S. Pipemo-Neumann[1,2], X.A. Cao[1], R. Couden[1], J.L. Breau[2], M.C. Jaurand[1], E. Taillandier[1]. [1]*Laboratoire de Spectrométrie Moléculaire, Université Paris XIII, Bobigny, France.* [2]*Service d'Oncologie Médicale CHU Avicenne, Bobigny, France*

Human malignant mesothelioma (MM) displays chromosomal abnormalities, particularly homozygous deletions of the p16 tumor suppressor gene.

In aherapt to replace altered genes in MM cell lines in culture and in nude mice xenograft, we developed a non viral gene delivery technique, using original synthetic cationic lipesomes V14 and V5, and a DNA compacting agent spermine. Transfection using naked DNA or commercialized cationic lipids is inefficient in MM cells. Cell lines were established from the MM of patients in accordance with pathological criteria, and prior to therapy.

The first step was to test the ability of different carriers: DOTAP, lipofectine, and original V5 and V14. Therefore, we studied the β galactosidase (βgal) gene expression in 3 human MM cell lines in culture (RAV, FER, BLA), after transfection of a βgal reporter gene (pCMVβ CLONTECH) complexed to lipids. 2.10^5 cells were transfected with 0.5 to 9 μg of pCMVβ alone, condensed with spermine, then complexed to cationic lipids. The βgal activity was measured by chemoluminescence (Galactolight® TROPIC) 48 hours after transfection. The

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